REMARKS

A check for the fees for a three month extension of time and an additional claim accompanies this response. Any other fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-8 and 19-31 are pending in this application. Claims 1, 2, 7, 8 are amended for clarity. Basis for the amendment can be found in the claims as originally filed. Claims 19-30 are added. Claims 19-31, find basis in the priority application, are added. Claim 8 is amended in accord with 37 C.F.R. § 1.75(c) to correct the claim dependency such that the claims, which are multiply dependent, do not depend from multiply dependent claims in accord with US practice. Claims 11-18, which were rejected as substantial duplicates of claims 1-10 are cancelled without prejudice or disclaimer.

The specification is amended to recite priority information needed upon entry of the application into the US national stage. The specification also is amended to insert SEQ ID NO: 1 following the amino acid sequence described on page 8, line 8, as required by the Examiner. Basis for the amendment is found in the Sequence Listing as originally filed. The specification is further amended to correct an obvious typographical error where an incorrect sequence listing identifier (SEQ ID NO: 1) was inadvertently provided for amino acid sequence SSPPPPC. As set forth in the sequence listing, SEQ ID NO: 1 lists amino acids 1-9 of the G17 peptide. SEQ ID NO: 2 recite the amino acid sequence: SSPPPPC.

A Declaration under 37 C.F.R. §1.132 of Dr. Watson, an inventor of this application has been prepared for her execution upon approval by her institution. The Declaration describes data presented in the application in Example 5, and additional clinical and *in vivo* data demonstrating the combining the immunotherapeutic approach to treating gastric and other gastrin-dependent cancers with chemotherapy does not reduce or eliminate the effectiveness of the gastrin immunogen as the prior art suggests it would. In addition, the combination permits lower doses of chemotherapy to be administered, thereby reducing toxicity of the chemotherapy. Thus, not only does the chemotherapy not impair the gastrin immunogen treatment, but the combination works together. As discussed below, the cited art, would have led the ordinarily skilled artisan to expect that chemotherapy would impair or destroy the effectiveness of the

gastrin immunogen. Those of ordinary skill in the art do no administer a gastrin immunogen, which requires an unimpaired immune system, in combination with chemotherapy.

INFORMATION DISCLOSURE STATEMENT

A supplemental Information Disclosure Statement is being filed under separate cover. It addresses the issue raised in the instant Office Action and provides cited references.

OBJECTIONS TO THE SPECIFICATION

The specification is amended to incorporate priority information and a sequence listing identifier page 8, line 8, as required by the Examiner.

THE REJECTION OF CLAIMS 5, 7, 12, 13, 14, and 17 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 5, 7, 12, 13, 14, and 17 are rejected under 35 U.S.C. §112, second paragraph, as indefinite on several grounds discussed in turn below. This rejection is moot with respect to claims 12, 13, 14 and 17. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Claim 5, and dependent claim 7, are alleged to be unclear because claim 5 recites that the gastrin-G17 peptide is SEQ ID No. 1 has 9 amino acids not 17 as indicated by the name of the peptide. . This rejection respectfully is traversed.

Claim 5 recites:

> . . . wherein the anti-gastrin G17 immunogen comprises a peptide that has the sequence of amino acid residues: pGlu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu as set forth in SEQ ID NO. 1.

Thus, claim 5 does not recite that gastrin-G17 contains 9 amino acids, but recites that the "anti-gastrin G17 immunogen" comprises the peptide whose sequence is set forth in SEQ ID NO. 1. The anti-gastrin G17 immunogen does not necessarily contain 17 amino acids, but as recited in the claim contains the 9 recited amino acids, and, by virtue of the open language can contain additional amino acids. Therefore, the claim is clear.

THE REJECTION OF CLAIMS 1, 7, 10, AND 16-17 UNDER 35 U.S.C. §102(b)

Claims 1, 7, 10, and 16-17 are rejected under 35 U.S.C. §102(b) as anticipated by Schoemaker *et al.* (European Patent No. 755683) because Schoemaker *et al.* discloses use of a monoclonal antibody that specifically binds to an epitope of 17-1A antigen for treatment of a

carcinoma. The Examiner states that the use of monoclonal antibody 17-1A for treating gastrointestinal tumors in combination with other chemotherapeutic agents is disclosed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). A reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The rejected claims

Claim 1 recites:

> A combination of anti-gastrin-dependent tumor therapeutic ingredients, comprising:
>
> (i) an immunogen directed against gastrin; and
>
> (ii) one or more chemotherapeutic agents.

Dependent combination claims recite particulars of the combination. Claims directed to methods employ the combination for treatment of tumors.

Analysis

Applicant does not concede that Examiner's recitation regarding the disclosure of Shoemaker *et al.* is correct. Whether or not it is correct, Schoemaker *et al.* does not disclose an immunogen directed against gastrin. Therefore, Schoemaker *et al.* does not disclose a combination of such immunogen and a chemotherapeutic agent. Thus, Shoemaker *et al.* does not disclose all elements as claims, and does anticipate claim 1 nor any pending claims.

THE REJECTIONS OF CLAIMS 1-18 UNDER 35 U.S.C. §103(a)

Claims 1-18

Claims 1-18 are rejected under 35 U.S.C. §103(a) as being unpatentable over Watson *et al.* (Cancer Research, Volume 56, 1996, page 880) in view of Morozov *et al.* (U.S. Patent No. 5,770,576) and Harrison *et al.* (Cancer, volume 66, 1990, page 1449, abstract) because Watson *et al.* teaches the use of Gastrimmune and Morozov *et al.* teaches that the chemotherapeutic agents, fluorouracil, leucovorin, levamisole, cisplatin, tumor necrosis factor, are known in the art and can be used in combination with other drugs. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use these agents in combination for treatment of colon cancer. This rejection respectfully is traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103 the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.,* 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch,* 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesh, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). There must be a reason why a person of ordinary skill in the art would have combined the elements as claimed. KSR v. Teleflex, Inc. 550 US _____ S.Ct. (2007).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The rejected claims

Independent claim 1 is directed to a combination:

(i) an immunogen directed against gastrin; and

(ii) one or more chemotherapeutic agents.

Dependent claims specify particulars regarding the components of the combination.

Claim 8 is directed to a method of treatment of a gastrin-dependent tumor, by administering the components of the combination. Claim 19 recites that the method is effected by administering an anti-gastrin-17 (G17) immunogen to immunologically neutralize gastrin; and administering an effective amount of one or more chemotherapeutic agents. Other dependent claims specify particulars of the immunogen or chemotherapeutic agent or methods.

Hence the claims are directed to the combination of an immunotherapeutic agent and a chemotherapeutic agent and use thereof for treating tumors. As described in the application (also in the art cited by the Examiner, and discussed below), chemotherapeutic agents are known to immunocompromise or impair the immune systems of treated subjects. Treatment with an immunogen requires an active immune system. Thus, one of ordinary skill in the art would have expected treatment with chemotherapy to ameliorate or eliminate the effectiveness of immunotherapy, treatment with an anti-gastrin immunogen, for treatment of gastrin-dependent cancers. As discussed below, and shown in the application (see, *e.g.*, Example 5), the combination of chemotherapy and anti-gastrin immunogen therapy is effective and in fact is synergistic. A Declaration of Dr. Susan Watson providing additional data demonstrating this synergy will be submitted under separate cover.

Analysis

Watson *et al.*

Watson *et al.* teaches that administration Gastrimmune polypeptide, a gastrin immunogen, results in antibodies that neutralize amidated and glycine-extended gastrin and

inhibit the growth of colon cancer. Watson *et al.* does not teach nor suggest combining Gastrimmune immunotherapy with chemotherapy.

Morozov *et al.*

Morozov et al. teaches methods for treating immunocompromised subjects by administering a dipeptide R'-Glu-Trp-R'', which is shown to increase expression of accessory molecules on the surface of thymocytes and mature T-lymphocytes. Morozov *et al.* teaches administration of the dipeptide R'-Glu-Trp-R" in conjunction with various chemotherapeutic agents in order to ameliorate the clinical symptoms resulting from chemotherapy. Hence Morozov *et al.* teaches that chemotherapy immunocompromises treated subjects. Morozov *et al.* provides no teaching or suggestion for administration of chemotherapy in combination with an ***immunotherapeutic*** agent that requires a robust immune system. In fact, Morozov *et al.* appears to teach away from such combination, since Morozov *et al.* teaches that chemotherapy comprises the immune system. One of ordinary skill in the art, thus, would believe (as taught in the instant application) that the combining chemotherapy with a gastrin immunogen would reduce the immune response, and effectiveness of the gastrin immunogen in treating the cancer.

Hence the combination of Watson *et al.*, which teaches that an immunotherapeutic approach to treating colon cancer, with the teachings of Morozov *et al.* would have suggested to one of ordinary skill in the art that chemotherapy would decrease or negate the effectiveness of Gastrimmune polypeptide therapy.

Harrison *et al.*

Harrison *et al.* teaches the effect of the CCK-B/gastrin receptor partial antagonist proglumide on survival in gastric carcinoma. Proglumide, which is 4-benzamido-N, N-dipropylglutamic acid, is a drug that inhibits gastric secretion. Harrison *et al.* reports that proglumide had **no** overall effect on survival of treated subjects. Harrison *et al.* also teaches that chemotherapy and radiotherapy have limited value in treating gastric carcinoma because of their toxicity and lack of efficacy (see, column 1, page 1449). Hence Harrison *et al.* is of no relevance to the instant claims, except to suggest that chemotherapy is of little benefit in treating gastric cancers. Harrison *et al.* certainly does not suggest combining immunotherapy for cancers with chemotherapy.

The combination of teachings of Watson *et al.*, Morozov *et al.* and Harrison *et al.* does not result in the instantly claimed methods

The combination of teachings of the references fails to teach or suggest combining tumor therapy with an anti-gastrin immunogen with chemotherapy. Watson *et al.* fails to teach or suggest combination therapy. Morozov *et al.* teaches that chemotherapy comprises the immune system, Harrison *et al.* indicates that chemotherapy is of little benefit in treating gastric cancers. Thus, the combination of teachings of references indicates that combined immunotherapy with a gastrin immunogen with chemotherapy would be of little therapeutic effect. Chemotherapy would be expected to abrogate the effectiveness of therapy with an anti-gastrin immunogen.

Contrary to these teachings, however, the application and Declaration (to be provided) demonstrate that combination therapy is effective and can be synergistic. Unexpected properties cannot be ignored; they are part of the invention as a whole. It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Wright*, 848 F.2d 1216, 6 USPQ2d 1959 (Fed. Cir. 1988); *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). As discussed above, the application (Example) shows that combining chemotherapy and treatment with a gastrin immunogen not only does not impair the effectiveness of treatment with gastrin, but results in improved therapeutic effect. Further, the application shows that the effect is synergistic in that lower doses of chemotherapy can be administered, which are less toxic. In addition, while not necessary, the Declaration, when executed, provides additional data showing these effects.

The combination of teachings of the cited references would not result in an expectation that treatment with an anti-gastrin immunogen would be effective when combined with chemotherapy. The cited art teaches that chemotherapy is immunosuppressive (Morozov *et al.*) and that it is ineffective for gastric tumors (Harrison *et al.*). The results shown in the application and in the Declaration show that this is not the case for combination therapy with an anti-gastrin immunogen and chemotherapy. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 1, 7, 10, and 15-18

Claims 1, 7, 10, and 15-18 are rejected under 35 U.S.C. §103 as being unpatentable over Schoemaker *et al.* (European Patent No. 755683) in view of Morozov *et al.* (U.S. Patent No.

5,770,576) and Harrison *et al.* (Cancer, volume 66, 1990, page 1449, abstract) because Schoemaker *et al.*, teaches use of monoclonal antibody 17-IA for treating gastrointestinal tumors and these can be used in combination with other chemotherapeutic agents (page 2, lines 15-23). This rejection is respectfully traversed. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

This rejection respectfully is traversed.

Analysais

The teachings of the references are discussed above. Briefly, Schoemaker *et al.* does not teach an immunogen directed against gastrin ; and Morozov *et al.* teaches that chemotherapy comprises the immune system; Harrison *et al.* teaches that proglumide has **no** overall effect on survival of treated cancer patients and that chemotherapy and radiotherapy have limited value in treating gastric carcinoma because of their toxicity and lack of efficacy

The combination of teachings of Schoemaker *et al.*, Morozov *et al.* and Harrison *et al.* does not result in the instantly claimed methods

The combination of teachings of the references fails to teach or suggest the claimed combinations. The combination of references fails to teach or suggest an immunogen directed against gastrin, and further fails to teach or suggest combining an immunotherapic approach to cancer with chemotherapy. As discussed above, Morozov *et al.* indicates that chemotherapy compromises the immune system; and Harrison *et al.* teaches that chemotherapy is not effective against gastric cancers. Consequently, the combination of teachings does not and cannot result in the instantly claimed combinations and methods. Further, none of these references, singly or in combination teaches or suggests that combined chemotherapy and immunotherapy can be effective, and that they can provide synergistic benefits as described in the application and also in the forthcoming Declaration of Dr. Watson.

THE REJECTION OF CLAIMS 1, 4-11, 15 and 79-81 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-2, 6-7, 10, 11, 13, 15, and 16-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 5, 12, 14-16, and 18-19 of copending U.S. Application Serial No. 11/360,378. This rejection respectfully is traversed.

Relevant law

Where a rejection is made between two pending applications, obviousness-type double patenting cannot be resolved until one application has issued and there are allowable claims in the other application, or at least until there are allowable claims in on of the applications so that the order in which the applications will issue is known. Double-patenting is only relevant to the later issuing application and only is based upon the claims in the two cases. Furthermore, if the order of issuance results from delays in the Patent Office, not from actions of the applicant, then a two-way distinctness test must be applied. See, In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991) in which the CAFC held that in certain circumstances a third inquiry to support an obviousness-type double rejection will only be sustained if the application claims are not patentably distinct from the prior patent claims and the prior patent claims are also not patentably distinct from the applications claims.

An "obviousness-type" double patenting rejection on the ground the claimed invention is unpatentably obvious over the claims of a U.S. patent having a common inventor is a judicially created doctrine, rather than a rejection based on the precise terms of 35 U.S.C. §101. *In re Longi et al.* (CAFC 1985) 759 F2d 887, 225 USPQ 645; *Ex parte Winquist et al.* (POBA 1972) 177 USPQ 472. It renders not validly patentable a "mere variation" of the prior patented invention which would have been obvious to those of ordinary skill in the relevant art. *Rafac International Ltd. v. Matsushita Electric Corp.* (DC NJ 1990) 17 PQ2d 1293.

The disclosure of a patent cited in support of a double patenting rejection cannot be used as though it were prior art even where the disclosure is found in the claims. Obviousness-type double patenting signifies that the difference between first-patented invention and its variant involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. Comparison can be made only with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference. A fundamental rule of claim construction requires that what is claimed is what is defined by the claims taken as a whole, every claim limitation (each step) is material. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 23 USPQ 1839 (Fed. Cir. 1992).

Double-patenting has not been found in instances in which the claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue. See, *e.g., Ortho Pharmaceutical Corp v. Smith*, 22 USPQ2d 1119 (Fed. Cir. 1992), in which obviousness-type double patenting was not found in an instance in which the claims in the patent at suit were directed to compounds that did not encompass, structurally, the compounds claimed in the prior patents, and the compounds claimed in the prior patents did not suggest a modification of those compounds to produce compounds claimed in the patent at suit.

Thus, obviousness-type double patenting does not exist if the claims at issue do not encompass the claimed subject matter in the co-pending application, and, the claims in the co-pending application do not suggest a modification to produce the claims in the subject application.

The test is whether the patent term (assuming that patent term for the issued patent expires before term for the claims) for the species covered by the claimed subject matter in the application at issue would extend coverage for that species in the issued patent. This can only be determined by applying principles of claim interpretation, not by using the prior patented claim as though it were art. If a generic claim has issued and the claim at issue is a species thereof, obviousness-type double patenting **cannot** be held unless the claim at issue is a minor obvious variant of the issued claim and of substantially the same scope. "Domination," which occurs when one patent includes generic claims and a second includes a species of the genus, does not give rise to double patenting.

The claims

The claims in the copending application, which was filed on February 22, 2006, claiming priority as a continuation to U.S. application Serial No. 10.104,607, filed March 22, 2002, which claims priority to U.S. provisional application Serial No. 60/278,294, fled March 23, 2001, are directed to combinations of an anti-gastrin immunogenic composition and a chemotherapeutic agent, and to methods of treatment of pancreatic cancer.

The instant application which is the US national stage of International PCT application No. US99/10750, filed May 14, 1999, which claims priority to a provisional application filed

May 15, 1998, includes claims directed to similar combinations, and to methods of treatment of gastrin-dependent cancers. Pancreatic cancer is a species of gastrin-dependent cancer.

Analysis

As noted above, since claims are amended during prosecution, obviousness-type double patenting cannot be assessed until there is allowable subject matter. Further, obviousness-type double patenting, only is relevant to the later issuing application. As a threshold issue, the instant application was filed 5 years before the copending application. Assuming Applicant timely responds to all Actions, absent, delays by the Patent Office, this application is likely to issue first. Hence, obviousness-type double patenting is not apt, nor is appropriate, at this time to file any terminal disclaimers.

Conflicting claims

Claims 1-2, 6-7, 10, 11, 13, 15, 16-1 9 are directed to an invention allegedly not patentably distinct from claims 1-2, 4, 5, 12, 14-16 and 18-1 9 of commonly assigned U.S. application Serial No. 11/360,378. The Examiner alleges that U.S. application Serial No. 11/360,378 would form the basis for a rejection of the noted claims under 35 U. S. C. 103(a)if the commonly assigned case qualifies as prior art under 35 U. S. C. 102(e), (f)or (g)and the conflicting inventions were not commonly owned at the time the invention in this application was made. This rejection is respectfully traversed in part. Deferral of resolution of the issue with respect to the combination claims respectfully is requested until Applicant has an opportunity to amend the claims in the copending application.

As noted above, copending U.S. application Serial No. 11/360,378, was filed on February 22, 2006, claiming priority as a continuation to U.S. application Serial No. 10/104,607, filed March 22, 2002, which claims priority to U.S. provisional application Serial No. 60/278,294, fled March 23, 2001. Hence the earliest priority date of the copending application is March 23, 2001.

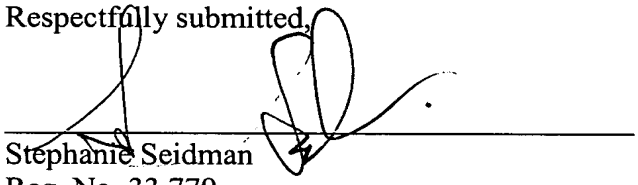
The instant application, which is the US national stage of International PCT application No. US99/10750, filed May 14, 1999, which claims priority to a provisional application filed May 15, 1998, includes claims directed to similar combinations, and to methods of treatment of gastrin-dependent cancers. Hence, the latest possible priority date of claims in the instant application is May 14, 1999, which is almost 2 years before the priority date of the copending

application. Accordingly, the copending application is not prior art by virtue of 35 U.S.C. §102(e). With respect to 35 U.S.C. §§102(f) and 102(g), the claims in the copending appear to be drafted in the form of first medical use claims in which the use does limit the claim. Upon receipt of an Action in the copending application, the combination claims will be amended.

* * *

In view of the above, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,



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